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Commentary

The Myocardial Ischemia Reduction with Acute Cholesterol Lowering (MIRACL) trial: a new frontier for statins?

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Abstract

The Myocardial Ischemia Reduction with Acute Cholesterol Lowering (MIRACL) Trial tested the hypothesis that intensive lowering of cholesterol with atorvastatin (80 mg/day) initiated 24–96 h after an acute coronary syndrome would, over 4 months, reduce the incidence of the composite endpoint of death, nonfatal infarction, resuscitated cardiac arrest, and recurrent symptomatic myocardial ischemia with new objective symptoms requiring emergency rehospitalization. This primary composite endpoint was reduced from 17.4% to 14.8% ($P = 0.048$) among the 3086 patients enrolled. The results of MIRACL suggest that patients with acute coronary syndromes should begin to receive this treatment before leaving hospital, irrespective of baseline levels of low-density lipoprotein-cholesterol.

Keywords atorvastatin, 3-hydroxy-3-methylglutaryl CoA reductase inhibitor, myocardial infarction, unstable angina

Aspirin, β-blockers, angiotensin-converting enzyme inhibitors, and statins have each been shown to improve the outcome of patients with coronary artery disease. The benefit of each of these drugs is generally pervasive, spanning a wide spectrum of patients. However, we might not have been aggressive enough in exploring the limits of the benefits that these treatments confer. One gap in the extensive clinical trial evidence supporting the use of these therapies is that statins have never been tested in patients with acute coronary syndromes. There is compelling evidence that statins reduce coronary events in the setting of both primary and secondary prevention. However, patients were excluded from previous secondary prevention trials with statins if they had experienced myocardial infarction or unstable angina within the preceding 3–6 months.

This 'knowledge gap' has perhaps contributed to a 'treatment gap'. Although it is clear that patients who have suffered an acute coronary event would obtain long-term benefit from cholesterol-lowering therapy, it continues to be the last thing that physicians do [1]. The focus tends to settle on mechanical therapies to relieve flow-limiting stenoses or antiplatelet and antithrombotic drugs that reduce recurrent events over the short term. Most patients leave hospital after an acute coronary event without receiving a statin or any other cholesterol-lowering drug. In fact, only 31.7% of 138,001 patients discharged from 1470 hospitals in the USA during a recent 12-month period received a cholesterol-lowering drug [2].

Recent evidence suggests that lowering low-density lipoprotein (LDL)-cholesterol favorably influences pathophysiological mechanisms that may be intimately involved in the genesis of acute coronary syndromes [3–5]. Intensive LDL-cholesterol reduction has the potential to improve endothelial function within hours [3] by reducing the production of superoxide anion within the vessel wall, thus facilitating the release of nitric oxide and slowing its rate of catabolism. Cholesterol lowering also normalizes the tendency to increase the deposition of platelet thrombus, a

LDL = low-density lipoprotein; MIRACL Trial = Myocardial Ischemia Reduction with Acute Cholesterol Lowering Trial.

feature of hypercholesterolemia [4]. A third important consequence of cholesterol lowering is a decrease in inflammation at the sites of atherosclerotic lesions, resulting in a decrease in circulating inflammatory markers [5]. The MIRACL trial tested whether or not these mechanisms have clinical relevance.

Results of MIRACL

At 122 sites in 19 countries, 3086 patients with unstable angina or non-Q-wave infarction were randomized to placebo or to atorvastatin (80 mg/day) within 24–96 hours of admission to hospital [6,7]. The main exclusion criteria were planned revascularization, a total cholesterol level greater than 270 mg/dl, or a contraindication to statin therapy. There was no lower limit for either total cholesterol or LDL-cholesterol. The mean LDL-cholesterol level on treatment was 135 mg/dl in the placebo group and 72 mg/dl in the atorvastatin group. The primary, predefined endpoint was the time to death, myocardial infarction, resuscitated cardiac arrest, or worsening angina with new objective evidence of myocardial ischemia requiring urgent rehospitalization. This composite endpoint was reduced from 17.4% to 14.8%, a relative reduction of 16% ($P = 0.048$). Although each of the components of the primary endpoint was reduced, most of the benefit was derived from a 26% relative decrease in worsening angina with objective evidence of myocardial ischemia requiring urgent rehospitalization ($P = 0.02$). Stroke, a secondary endpoint, was reduced by 50%, from 1.6% to 0.8%, with atorvastatin ($P = 0.045$).

In contrast to the previous major primary and secondary prevention trials with statins, in which the duration of follow-up was at least 4–5 years, the duration of treatment in the MIRACL trial was 4 months. A second important feature of the trial was that it tested the effects of a statin at the time when coronary events are highest: soon after an episode of unstable angina or non-Q-wave infarction. The short duration of therapy and high event rate during this interval combine to make this treatment extremely cost-effective. For approximately $500 in drug costs per patient, the event rate during 4 months of treatment was reduced by 2.6%, a cost:benefit ratio that compared favorably with that seen in long-term secondary prevention with statins [8]. This difference of 2.6% in absolute event rates corresponds to a number needed to treat to prevent one event in approximately 38.

Like all innovative clinical trials, MIRACL raises many interesting questions, some of which will be discussed here.

Would benefit extend to all patients with acute coronary syndromes?

Patients with Q-wave infarction were excluded from MIRACL because many of the events that they experience during follow-up are the result of left ventricular dysfunction or ventricular arrhythmias, processes that are unlikely to be influenced by a lowering of cholesterol level. However, it seems reasonable to expect that the reduction in recurrent ischemic events observed in MIRACL would also extend to this population.

Patients scheduled to undergo revascularization were also excluded from the trial, on the presumption that coronary events related to initial and recurrent procedures might obscure any treatment effect. Revascularization is a focal strategy, whereas atherosclerosis is a diffuse arterial disease, and statin therapy has potential benefit throughout the entire arterial system. Many recurrent ischemic events (both coronary and cerebrovascular) result from instability at sites other than the original causal coronary lesion. Therefore, the benefits of revascularization and intensive lipid-lowering treatment would be expected to be complementary.

Is event reduction related to LDL-cholesterol lowering?

In previous primary and secondary prevention trials with statins, the investigators correlated the degree of benefit to baseline lipid levels and to the change in lipid levels with treatment. This approach is unlikely to be fruitful in MIRACL for several reasons: (1) baseline lipid measurements might have been transiently depressed owing to the acute coronary event; (2) lipid levels during treatment were first measured at 6 weeks, by which time many of the endpoint events had already occurred; (3) factors other than serum lipids have a greater effect on acute coronary syndromes than on stable coronary disease; and (4) the statistical power for subgroup analyses is low because the treatment effect was barely statistically significant for the whole trial.

Notwithstanding these limitations, there was no trend to suggest that atorvastatin treatment in MIRACL was of greater benefit in patients with higher baseline LDL-cholesterol levels. It is therefore reasonable to apply the MIRACL strategy irrespective of serum lipid determinations at the time of the acute coronary event.

In MIRACL, LDL-cholesterol levels during treatment differed by 52% between the placebo and atorvastatin groups. Would a lower dose of atorvastatin, or of any other statin, have produced the same degree of benefit? Answering this question conclusively would require a study in which patients with acute coronary syndromes were randomly assigned to receive these different therapies. In previous long-term cholesterol-lowering trials, involving different patient populations and different treatments, the reduction of acute coronary events was proportional to the degree of LDL-cholesterol reduction with active treatment [9].

Why was the treatment effect different for different endpoints?

The reductions in total mortality and in myocardial infarction were much smaller than the reductions in worsening angina with objective evidence or in stroke, and were not statistically significant. The trial was not powered to show a reduction in these individual endpoints, and the 95% confidence intervals for each of the four components of the primary composite endpoint overlapped broadly. MIRACL should be interpreted as showing a reduction in the composite endpoint rather than just in one or more of the components. Combining these endpoints is reasonable because they have, at least in part, a common pathophysiological basis and might all be expected to respond in the same way to treatment.

Do other trials test the effect of statins in acute coronary syndromes?

At least three other clinical trials that are currently under way will expand our knowledge of the effects of statins early after an acute coronary event. The Aggrastat to Zocor (A to Z) Trial includes an initial phase in which patients with unstable angina or myocardial infarction without ST-segment elevation are all treated with tirofiban and are randomized to enoxaparin or unfractionated heparin. Stabilized patients, including patients with ST-elevation myocardial infarction not included in the original randomization, are then randomized to either simvastatin (40 mg/day) or placebo. After 1 month the dose of simvastatin is increased to 80 mg/day; after 4 months, patients in the placebo arm begin taking simvastatin at 20 mg/day. The projected enrollment for the second phase of the trial is 4500 patients. Follow-up will continue until the occurrence of 970 endpoint events, defined as cardiac death, myocardial infarction, or readmission for an acute coronary syndrome.

The Prevention of Re-Infarction by Early Treatment of Cerivastatin Study (PRINCESS) will randomize 3000 patients with acute myocardial infarction within 48 hours of admission to receive either a placebo or 0.4 mg/day cerivastatin. At 3 months the dose will be increased to 0.8 mg/day and the placebo patients will begin taking 0.4 mg/day cerivastatin. The primary endpoint is a composite of fatal or nonfatal myocardial infarction, unstable angina, heart failure or cardiac death. A minimum follow-up period of 2 years is planned.

The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) Trial will randomize 4000 patients up to 10 days after an acute coronary syndrome to pravastatin (40 mg/day) or atorvastatin (80 mg/day), with a mean follow-up of 2 years. Patients with total cholesterol levels of 240 mg/dl or more will be excluded. Patients will also be randomized to the antibiotic gatifloxacin or to placebo, to determine whether antibiotics reduce recurrent coronary events.

Are there observational data on the use of statins in acute coronary syndromes?

Recent observational studies indicate that patients who are treated with a statin early after a coronary event have a much more favorable outcome than those who are not [10–12].

A prospective cohort study using data from the Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) showed that early initiation of treatment with statin in patients with acute myocardial infarction was associated with a reduced 1-year mortality [10]. The study compared 5528 patients who received statins at or before hospital discharge with 14,071 who did not. At 1 year, mortality was 4.0% in statin users and 9.3% in non-users. This difference narrowed considerably after adjustment for confounding factors. However, early treatment with statin was still associated with a reduction in 1-year mortality, with a relative risk of 0.75 (95% confidence intervals 0.63–0.89, $P = 0.001$).

Retrospective analyses of clinical trial databases of patients with acute coronary syndromes have also shown this pattern. A report examining the 20,809 patients in the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) and Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trials, who were discharged from hospital after an acute coronary syndrome, revealed that those treated with a lipid-lowering drug exhibited a survival advantage that was already apparent at 1 month [11]. The adjusted risk ratio for 6-month mortality was 0.67 (95% confidence intervals 0.48–0.95, $P = 0.023$). Similarly, in a preliminary report from Orbofiban in Patients with Unstable coronary Syndromes – Thrombolysis in Myocardial Infarction (OPUS-TIMI 16), mortality at 1 month was reduced in patients treated with lipid-lowering drugs (94% of which were statins) compared with those who were not: 0.7% versus 2.4% ($P < 0.001$) [12].

In each of these three observational studies, patients who were treated with lipid-lowering drugs were younger and healthier than patients who were not given this treatment. The apparent benefit from early statin therapy decreased in each population after adjustment for variables known to affect prognosis. Physicians are probably much less likely to prescribe statins after an acute coronary event in patients perceived to have a poor prognosis. This selection bias might account for not just a part but for all of the apparent benefit observed with statin use in these three studies. As in other situations, randomized trials of statin therapy, started early after an acute coronary event, are necessary to determine whether this approach has merit.

How should MIRACL influence clinical practice?

Taken together with the evidence from previous secondary prevention trials, MIRACL should convince even the most stubborn that treatment of unstable angina and non-Q-wave infarction should include a statin, should begin in the hospital, and should be given irrespective of baseline LDL-cholesterol levels. One dose of one statin was tested in MIRACL. Whether similar benefit would accrue from smaller dosages or with other statins will in part be answered by the other trials of statins in acute coronary syndromes.

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